REMARKS

This is a full and timely response to the Office Action mailed April 9, 2007, submitted concurrently with a three month Extension of Time to extend the due date for response to October 9, 2007.

By this Amendment, claims 1-5, 7-13 and 20 have been canceled without prejudice or disclaimer to their underlying subject matter. Further, claims 16 and 21 have been amended to address the rejection under 35 U.S.C. §112, second paragarph. Still further, claim 17 has been amended to clarify that the metal complex is used for determining amino acid sequence of protein or peptide, recite the feature of canceled claim 1 (i.e. "*wherein the covalent bond to be formed between the amino group of the N-terminal amino acid residue of protein or peptide and the functional group is not cleaved in a stage of ionization in mass spectrometry*"), and limit the substituent of the ligand L1 to $-R_2-CO-OR_1$ and R_2 to a phenylene group. In addition, claim 19 has been amended to clarify that the metal complex is used for determining amino acid sequence of protein or peptide, recite the feature of canceled claim 1, and limit the substituent of the ligand L_3 to $-R_2-NH_2$ or $-R_2-NHNH_2$ and R_2 to a phenylene group. Lastly, claims 14-16 have been amended, and new claims 22-24 have been presented to direct to independent claims 17 and 19. Support for the claim amendments and new claims can be found variously throughout the specification and the original claims. Thus, claims 14-19 and 21-24 are pending in this application.

In view of this amendment and the following remarks, Applicant believes that all pending claims are in condition for allowance. Reexamination and reconsideration in light of the above claims and the following remarks is respectfully requested.

Rejection under 35 U.S.C. §112

Claims 16 and 21 are rejected under 35 U.S.C. §112, second paragraph, for alleged indefiniteness. Applicant respectfully traverses this rejection.

The Examiner has maintained the rejection of the term "*derivative*" despite Applicant's claim amendments and arguments. The Examiner believes that the term "*derivative*" does not clearly define how similar a compound should be to the base compound to be called derivative. More specifically, the Examiner notes that there is no distinctive recitation regarding

the closeness or distinctiveness of the base compound structure, formula, molecular weight and other physical or chemical properties with the term "*derivative*".

However, contrary to the Examiner's statements in this regard, Applicant strongly believes that in view of the other limitations in the claims (i.e. "*reacting a metal complex which comprises a functional group which has a property of forming a covalent bond with an amino group of an N-terminal amino acid residue of protein or peptide or with a carboxyl group of a C-terminal amino acid residue of protein or peptide, with a protein or peptide (A) of which the amino acid sequence is to be determined, to form a derivative (B) of said metal complex where the covalent bond of the functional group of the metal complex with the amino group of the N-terminal amino acid residue of the protein or peptide (A) or with the carboxyl group of the C-terminal amino acid residue of protein or peptide is formed*"), the metes and bounds of the term "*derivative*" is very clear when read in context.

The method for determining an amino acid sequence of claims 16 and 21 clearly defines the derivative as a metal complex covalently bonded (*via a functional group on said metal complex*) to either the amino group of the N-terminal amino acid residue or the carboxyl group of the C-terminal amino acid residue of a protein or peptide. In the specification and claims, each of the components, structure, and properties of the metal complex (i.e. *functional group, metal element, ligand, coordination number*) is described (see pages 8-16 of the specification). Further, the components (*amino acids*), structure (*chains of amino acids linked together by peptide bonds with an amino group at the N-terminal and a carboxyl group at the C-terminal*) and properties of a peptide or protein is well known to one skilled in the art. Thus, Applicant strongly believes that the components (*1. metal complex and 2. peptide or protein*), structure (*metal complex covalently bonded to either an amino group or the carboxyl group of a protein or peptide*) and properties (for example, *functional group not cleaved in a stage of ionization in mass spectrometry*) of the claimed derivative is clearly described in claims 16 and 21 when read in context to the teachings in the claims and specification.

Nevertheless, to further address the Examiner's concerns in this regard and in view of the comments above, Applicant has amended claims 16 and 21 to include the phrase "*wherein the derivative comprises said metal complex covalently bonded via a functional group on said metal complex to either the amino group of the N-terminal amino acid residue or the carboxyl group of the C-terminal amino acid residue of said protein or peptide.*"

Thus, in view of the comments above and the amendments to the claims, withdrawal of this rejection is respectfully requested.

Rejection under 35 U.S.C. §103

Claims 1-5 and 7-21 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over Gariepy (WO 93/23425) in view of Anderson et al. (U.S. Patent No. 5,439,829) and further in view of Liao et al. (Journal of American Society of Mass Spectrometry, Volume 8, pages 501-509, 1997). With regard to claims 1-5 and 7-13, this rejection has been rendered moot in view of the cancellation of these claims. With regard to claims 14-19 and 21, Applicant respectfully traverses this rejection.

To establish a *prima facie* case of obviousness, the following three criteria must be satisfied. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. Here, in this case, based on Applicant's review of the cited references and the Examiner's comments, Applicant submits that the above criterias have not been satisfied. In particular, Applicant believes that the cited references fail to teach or suggest all the claim limitations with particular emphasis on the limitations "*wherein the metal complex is represented by the following general formula (I): $(L_2)mM(L_1)$ (I), wherein M represents a transition metal; L_1 represents a ligand having a substituent: **$-R_2-CO-OR_1$** **(where R_2 represents a phenylene group**, R_1 represents H or an active ester-forming group); L_2 represents a ligand; m is a number of L_2, indicating 0, 1, 2, 3, 4 or 5*", and "*wherein the metal complex is represented by the following general formula (III): $(L_2)mM(L_3)$ (III), wherein M represents a transition metal; L_3 represents a ligand having a substituent: **$-R_2-NH_2$ or $-R_2-NHNH_2$ (where R_2 represents a phenylene group)**; L_2 represents a ligand; m is a number of L_2, indicating 0, 1, 2, 3, 4 or 5*".

Gariepy is directed only to a metal chelating peptide which can be coupled to a targeting molecule to deliver to a desired site (*in vivo* or *in vitro*) for a diagnostic or therapeutic purposes (see page 1, 1st and 3rd paragraph of Gariepy). Gariepy does not at all disclose or suggest determining the amino acid sequence of protein or peptide using mass spectrometry.

Further, Gariepy never discloses or suggests *a phenylene group* substituted to the ligand in Gariepy's metal chelating peptide.

Likewise, Anderson et al., which is directed to CP-IMAC (see column 2 of Anderson et al.), also fails to disclose or suggest determining the amino acid sequence of protein or peptide using mass spectrometry. In addition, Anderson et al. also does not disclose *a phenylene group* as a spacer in Anderson's compounds represented by a formula [BAM-(spacer)$_x$-chelator]$_n$-(M)].

In addition, like Gariepy and Anderson et al., Liao et al., which is directed to charge remote fragmentation pr peptides following attachment of a fixed positive charge (i.e. tris[(2,4,6-trimethoxyphenyl)phosphonium]acetylgroup) and MALDI-PDS (see page 501, title and abstract, of Liao et al.), also never disclose or suggest a metal chelate complex. Therefore, Liao et al. does not disclose or suggest *a phenylene group* in the attachment of the fixed positive charge.

In contrast to these cited references, the present invention of the claims (see claims 17 and 19) is directed to a metal complex for determining the amino acid sequence of a protein or peptide comprising a ligand having *a phenylene group* as a substituent. Therefore, it is clear that the combination of Gariepy, Anderson et al. and Liao et al. does not disclose or suggest all the limitations of the amended claims.

It should also be noted that with regard to a metal complex (the type 1) having a functional group capable of forming a covalent bond with the amino group of the N-terminal amino acid residue of protein or peptide (see page 10, line 20, of the specification), a phenylene group is preferably employed in view of the easiness in nucleophilic reaction with the amino group (see page 11, lines 15-17, of the specification).

Applicant wishes to emphasize that the metal complex in the present invention enables extremely rapid and highly sensitive (about 100 fmol) sequencing (see page 19, lines 12-24, of the specification). 100fmol scale corresponds to the amount of samples separated using two-dimensional gel electrophoresis, and therefore the sequencing method using the metal complex of the present invention is of an extremely high utility. In contrast, Applicant wishes to note that the sequencing method of Liao et al. is only performed in 10pmol scale (see page 508, Figure 5, of Liao et al.).

The phenylene group in the metal complex of the present invention (which is preferably employed in view of the easiness in nucleophilic reaction with the amino group as described above) allows a metal complex derivative (i.e. protein of peptide labeled with the

metal complex, which is subjected to measurement by mass spectrometer) to be obtained in high yield. This means that the metal complex enables the determination of an amino acid sequence in an extremely small scale such as 100 fmol. In addition, since the metal complex of the present invention raises the ionization efficiency in the step of mass spectrometry, the peptide fragment can be selectively detected by multi-stage MS analysis such as MS^5 analysis (see Example 2, Fig 4, of the specification).

Such superior and excellent results cannot be expected by one skilled in the art since the cited references fails to teach or suggest a metal complex comprising a ligand having *a phenylene group* as a substituent. As the Examiner already knows, a showing of superior and unexpected properties can rebut a *prima facie* case of obviousness. *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Consequently, Applicant believes that the present invention would not be obvious over the combined teachings and suggestions of Gariepy, Anderson et al. and Liao et al.

Further, the Examiner has responded to Applicant's previously submitted arguments by first stating that the phrase "*a rapid and highly sensitive method for determining the amino acid sequence of a protein or peptide through mass spectrometry*" is not found anywhere within the four corners of claims 1-5 and 7-21. Applicant would like to direct the Examiner's attention to the phrase "*wherein the covalent bond to be formed between the amino group (of the N-terminal amino acid residue of protein or peptide) or the carboxyl group (of the C-terminal amino acid residue of protein or peptide) and the functional group is not cleaved in a stage of ionization in mass spectrometry*" which is an critical aspect of the present invention to allow for the rapid and highly sensitive determination of the amino acid sequence through mass spectrometry. Further, the nearly identical phrases of "*a method for determining amino acid sequence of protein or peptide*" and "*through mass spectrometry*" is found in claims 16 and 21. Thus, contrary to the Examiner's conclusions, the noted phrase (with the exception of the terms "rapid and highly sensitive") is found within the four corners of claims 1-5 and 7-21

In addition, the Examiner defends his obviousness rejection by arguing that "*the motivation to combine said references is within the references because the references teach different aspects/steps of the claimed invention at the time that the said invention was invented*" (see page 5, line 21-23, of the action). In other words, it appears that the Examiner is arguing that motivation to combine references is automatically present in the references when the

references in combination teach all aspects of the present invention. However, such an argument is inconsistent with U.S. case law.

The finding of a "*motivation to combine*" is not based on a conclusion of whether the cited references teach, in combination, all the elements of the claimed invention but rather whether the teachings or suggestions of the cited references would motivate one skilled in the art to combine the elements disclosed in the cited references. Under U.S. case law, "[T]here are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet,* 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Without identifying the teachings in the cited references which would motivate one skilled in the art to combine the elements disclosed in the cited references (for example, the nature of the problem to be solved), a *prima facie* case of obvious cannot be established. It should be noted that in *In re Rouffet*, the combination of the cited references taught every element of the claimed invention, however, without a motivation to combine, a rejection based on a *prima facie* case of obvious was held improper.

In the present case, the Examiner has only identified where in the cited references, the claimed elements (for example, metal complex, mass spectrometry) are taught. The Examiner has not cited or discussed any teachings such as the nature of the problem to be solved in the cited references which would motivate one skilled in the art to combine the metal complexes of Gariepy and Anderson et al. with the MALDI spectrometry of Liao et al. in a method of determining an amino acid sequence.

The Examiner also makes the statement on page 5, lines 23-26, of the action that since "*the claimed invention is prima facie obvious over the Examiner-cited references, as a consequence, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.*" However, such a statement is also inconsistent with U.S. case law. U.S. case law requires at least some discussion as to why one skilled in the art based on the teachings of the cited references would have a reasonable expectation that the combined teachings of the cited references would be successful. The Examiner has only presented a conclusion of a reasonable expectation of success from an alleged *prima facie* showing of obviousness. However, such a conclusion cannot be made since to establish a *prima facie* case of obviousness, a reasonable expectation of success must be shown

(see §2142 of the MPEP). Thus, for these reasons, Applicant believes that the Examiner has not established a reasonable expectation of success.

Thus, for these reasons, withdraw of this rejection is respectfully requested.

Applicant also requests the Examiner to clarify his citation on page 6, lines 16 and 17, of the action since there is no office action mailed August 9, 2006 or item 14 in the office action dated July 31, 2006.

CONCLUSION

For the foregoing reasons, all the claims now pending in the present application are believed to be clearly patentable over the outstanding rejections. Accordingly, favorable reconsideration of the claims in light of the above remarks is courteously solicited. If the Examiner has any comments or suggestions that could place this application in even better form, the Examiner is requested to telephone the undersigned attorney at the below-listed number.

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Respectfully submitted,

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